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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,920	11/04/2003	Brenda F. Baker	ISIS-5203	7522
32650	7590	10/02/2006	EXAMINER	
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE - 46TH FLOOR PHILADELPHIA, PA 19103			VIVLEMORE, TRACY ANN	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/700,920	BAKER ET AL.
	Examiner	Art Unit
	Tracy Vivlemore	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 17 July 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-66 is/are pending in the application.
- 4a) Of the above claim(s) 11,12,14-31,33,34,43,44,46-63,65 and 66 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-10,13,32,35-42,45 and 64 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date see box 6.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application
- 6) Other: See Continuation Sheet.

Continuation of Attachment(s) 6). Other: IDS of 1/2/04, 4/14/04, 5/13/04, 8/11/04, 9/13/04, 12/13/04, 1/18/05, 1/27/05, 3/14/05, 3/21/05, 4/5/05, 4/15/05.

DETAILED ACTION

Election/Restrictions

Applicant's election of group I and the species election of the structures shown in claim 13 in the reply filed on July 17, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 11, 12, 14-31, 33, 34, 43, 44, 46-63, 65 and 66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 17, 2006.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The claims of the instant application are directed to compositions comprising two chemically synthesized oligomers that are at least partially complementary and comprise at least one C and U or T modified binding base wherein one of the oligomers is capable of hybridizing with a target nucleic acid. Application 10/078,949 is directed to oligomeric compounds that hybridize to a target nucleic acid. This application does not provide support for compositions comprising two chemically synthesized oligomers that are at least partially complementary. Therefore, the priority date accorded the generic claims of this application is November 5, 2002, the filing date of application 60/423,760. While the '760 application contemplates compositions of oligonucleotides comprising modified nucleotides including modified nucleobases, it provides no disclosure of the modified nucleobase of the elected species. Therefore, the priority date for claims 13 and 45 is the filing date of the instant application, November 4, 2003. If applicant believes 10/078,949 or 60/423,760 provides support for the instantly claimed invention it should be pointed out with particularity in any response to this action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 10, 13, 35-41 and 45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 14-17, 23, 24, 37-40 and 47-50 of copending Application No. 10/561,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '618 application are an obvious variation of the instant claims. The instant claims are directed to compositions of oligomers that comprise a modified nucleobase that is able to bind to C, U or T bases. These modified nucleobases include

modified purines such as 2 substituted purines. The claims of the '618 application are directed to compositions of oligomers comprising a modified nucleoside that confers enhanced affinity for a complementary nucleotide. Claims 14-17, 23 and 24 of the '618 application are directed to specific embodiments that comprise modified purine nucleosides, including purines substituted at the 2 position. Claims 37-40 and 47-50 recite limitations identical to those of instant claims 2-8 and 35-41.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-42, 45 and 64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claimed invention is directed to compositions comprising an oligomer having a C and U or T modified binding base and a protein that comprises at least a portion of a RNA-induced silencing complex (RISC).

The specification describes RISC as being a ribonucleoprotein complex that contains an oligonucleotide and proteins of the Argonaute family, among others. The specification further discloses eIF2C1 and eIF2C2 as exemplary Argonaute proteins. The art teaches that prior to and even after the time of filing the precise size and composition of a RISC complex has not been fully elucidated for any species even though several proteins such as those in the Argonaute family have been identified as components of RISC. See, for example, Meister et al. (Nature 2004), and Martinez et al. (Cell 2002, cited on IDS of 4/14/04).

Martinez et al. describe on pages 566-568 the partial purification of human RISC and identify two proteins, eIF2C1 and eIF2C2/GERp95 as components. Martinez et al. note on page 568 that other proteins present in human RISC are yet to be identified.

Meister et al. describe the state of the art with regard to the RISC of several species in late 2004. At page 344 Meister teaches that several forms of RISC differing in size and composition have been reported. At column 2 of this page the differences in mass of various RISCs are attributed to weak and/or transient association of proteins involved in initial processing of dsRNA and to "factors of unknown function". At page 346, second column Meister et al. teach that while it is known that RISC complexes catalyze hydrolysis of phosphodiester in the target RNA, the component of RISC that performs this hydrolysis is yet to be identified.

Based on the teachings of the prior and post-filing art that the components of the RISC complex are not fully known, the skilled artisan would recognize that neither the instant specification nor the knowledge in the art provide a representative sample of the genus of proteins that comprise a portion of the RISC complex. Therefore, the skilled

artisan would not be able to a priori visualize the structure of the genus of proteins corresponding to the function of comprising a portion of a RNA induced silencing complex.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

"An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

Therefore, the full breadth of proteins that comprise a portion of a RNA induce silencing complex encompassed by the claims do not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claims 32 and 64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claims 32 and 64 are directed to pharmaceutical compositions comprising the oligomeric compounds of the invention. While it is accepted that claims to a composition comprising a pharmaceutically acceptable carrier do not require the composition be used as a pharmaceutical, a claim directed to a pharmaceutical composition implies the composition is to be used as a therapeutic in an organism.

The specification discloses oligonucleotide comprising C and U or T modified binding bases and describes methods for their use in cells in culture to inhibit gene expression. The specification also provides a prophetic disclosure of how these oligonucleotides could be used *in vivo* to inhibit gene expression and treat disease. The specification provides no working examples describing the use of these oligonucleotides *in vitro* or *in vivo*.

Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. (*Nature Reviews Drug Discovery*, 2002, vol. 1, p. 503-514)). Such problems include the inability to specifically deliver an

effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Opalinska et al. state on page 511

"[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

"Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful therapeutic outcome. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art do not provide that guidance, such that the skilled artisan would be able to use the claimed oligomeric compounds for therapeutic purposes. The amount of experimentation required is such that one of skill in the art

could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 32 and 64 are not enabled. This rejection may be overcome by removing the word "pharmaceutical" from the preamble of these claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-10, 32, 35-42 and 64 are rejected under 35 U.S.C. 102(e) as being anticipated by Brown et al. (US 2004/0029275).

The claimed invention is directed to compositions of oligomers capable of hybridizing to a target nucleic acid and further comprising at least one C and U or T modified binding base, a modified purine nucleobase that can hybridize to C, U or T. In specific embodiments the oligomer is 12-50, 15-30 or 21-24 nucleotides in length or further comprises a protein comprising a portion of a RNA-induced silencing complex (RISC).

Brown et al. disclose siRNAs and methods of using these siRNAs to inhibit gene expression. At paragraph 21, Brown et al. disclose that the siRNAs can be 15-1000 nucleotides in length, while at paragraph 149 and in table 3 they disclose the siRNAs of

the invention comprise modified nucleobases such as deazapurine, 2,6-diaminopurine, 8-hydroxyguanine or 6-hydroxyaminopurine. At paragraph 18 Brown et al. disclose that the siRNAs of the invention associate with the RISC which includes formation of a composition comprising a siRNA and a protein comprising a portion of a RNA induced silencing complex.

Thus, Brown et al. disclose all limitations of and anticipate claims 1-10, 32, 35-42 and 64.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 13, 32, 35-42, 45 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. as applied to claims 1-10, 32, 35-42 and 64 above, and further in view of Cook et al. (US 5,459,255, cited on IDS of 4/14/04).

Claims 1-10, 32, 35-42 and 64 are described in the 102 rejection over Brown et al. Claims 13 and 45 depend from either claim 1 or claim 35 and recite particular C and U or T modified binding bases comprising 2 substituted purine bases.

Brown et al. teach siRNAs and methods of using these siRNAs to inhibit gene expression. At paragraph 21, Brown et al. teach that the siRNAs can be 15-1000 nucleotides in length, while at paragraph 18 Brown et al. teach that the siRNAs of the invention associate with the RISC which includes formation of a composition comprising a nucleobase modified siRNA and a protein comprising a portion of a RNA induced silencing complex. At paragraph 149 and in table 3 they teach the siRNAs of the invention comprise modified nucleobases such as deazapurine, 2,6-diaminopurine, 8-hydroxyguanine or 6-hydroxyaminopurine. Brown et al. do not teach their siRNAs comprise a modified purine having the structure shown in claims 13 and 45.

It was well known in the art at the time of invention that modified nucleobases are useful for stabilization of therapeutic nucleic acids. Cook et al. teach oligonucleotides having modified nucleobases in the form of 2-substituted purines. At column 3-4, Cook et al. teach that these nucleobases do not affect duplex stability but do exhibit increased affinity for a complementary strand as compared to the unsubstituted nucleobase.

It would have been obvious to one of ordinary skill in the art at the time of invention to make the siRNAs comprising modified nucleobases taught by Brown et al. with the modified nucleobases taught by Cook et al. Brown et al. provide a motivation

to make siRNAs comprising modified nucleobases by explicitly suggesting such modifications. Cook et al. provide a motivation to make an oligonucleotide comprising 2-substituted purines by teaching that such substitution provides an oligonucleotide with increased affinity for a target nucleic acid. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Brown et al. and Cook et al. because methods of producing modified oligonucleotides are well-known and routinely used in the art.

Thus, the invention of claims 1-10, 13, 32, 35-42, 45 and 64 would have been obvious, as a whole, at the time of invention.

Claims 1-10, 13 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (WO 94/01550, cited on IDS of 4/5/05) in view of Cook et al. (US 5,459,255, cited on IDS of 4/14/04).

The claimed invention is directed to oligomeric compounds capable of hybridizing to a target nucleic acid comprising two complementary strands and further comprising at least one C and U or T modified binding base, a modified purine nucleobase that can hybridize to C, U or T. In specific embodiments the oligomers are a pair of siRNA oligomers of a pair of sense/antisense oligomers that are 12-50, 15-30 or 21-24 nucleotides in length or the modified base has the structure shown in claim 13.

Agrawal et al. teach self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. The oligonucleotides can comprise deoxyribonucleotides, ribonucleotides, or a combination thereof. On page 15 Agrawal et al. teach that the self-complementary region of the oligonucleotide is fully or partially

complementary to the hybridizing region while at page 9, line 30 through page 10 line 1 it is taught that the target hybridizing region comprises 8 to 50 nucleotides and is complementary to a nucleic acid sequence from a variety of sources including viruses, pathogens, cellular genes or gene transcripts. Pages 15 and 16 describe embodiments where the oligonucleotide is a single nucleic acid strand that forms a double stranded structure as well as an embodiment where the self-complementary region is connected to the hybridizing region by a non-nucleotide linker, making the self-complementary region and the hybridizing region two separate complementary nucleic acid strands. At page 16, Agrawal et al. teach that the oligonucleotides of their invention comprise nucleotide modifications that enhance nuclease resistance and/or cellular uptake and/or affinity of the oligonucleotide for its target. Agrawal et al. do not explicitly teach the use of C and U or T modified binding bases such as those in claim 13 as a nucleotide modification.

It was well known in the art at the time of invention that modified nucleobases are useful for stabilization of therapeutic nucleic acids. Cook et al. teach oligonucleotides having modified nucleobases in the form of 2-substituted purines. At column 3-4, Cook et al. teach that these nucleobases do not affect duplex stability but do exhibit increased affinity for a complementary strand as compared to the unsubstituted nucleobase.

It would have been obvious to one of ordinary skill in the art at the time of invention to make the self-stabilized oligonucleotides taught by Agrawal et al. with the modified nucleobases taught by Cook et al. Agrawal et al. provide a motivation to make self-stabilized oligonucleotides with nucleotide modifications by explicitly suggesting such modifications. Cook et al. provide a motivation to make an oligonucleotide

comprising 2-substituted purines by teaching that such substitution provides an oligonucleotide with increased affinity for a target nucleic acid. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Agrawal et al. and Cook et al. because methods of producing modified oligonucleotides are well-known and routinely used in the art.

Thus, the invention of claims 1-10, 13 and 32 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

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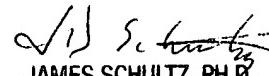
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Tracy Vivlemore
Examiner
Art Unit 1635

TV

September 25, 2006


JAMES SCHULTZ, PH.D.
JAMES PRIMARY EXAMINER
PRIM.